BIOMEDICINE

Ferroptosis—disease perils and therapeutic promise

Mechanisms of iron-dependent cell death reveal potential new targets for disease treatment

By **Ashley R. Brown[1], Tal Hirschhorn[1], Brent R. Stockwell[1,2,3,4]**

Recent discoveries involving cell death and metabolism are beginning to elucidate mechanisms involved in intractable diseases. Ferroptosis is a form of cell death driven by iron-dependent damage to lipids, the building blocks of cellular membranes. Specifically, lipids that contain polyunsaturated fatty acids readily undergo oxidation, causing damage to membranes. If not eliminated by intracellular repair mechanisms, such as the enzyme glutathione peroxidase 4 (GPX4), high concentrations of oxidized lipids can lead to membrane rupture and ultimately to cell death. Ferroptosis is regulated by multiple cellular processes, including iron regulation, lipid metabolism, and antioxidant defense systems. It has been implicated in a range of pathologies, including neurodegeneration, cancer, and organ injury. These and other conditions bearing signatures of ferroptosis—including iron accumulation, an increase in reactive oxygen species, and lipid oxidation—may be amenable to ferroptosis-modulating treatments.

The notion that ferroptosis drives neurodegeneration is emerging from studies of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). In the case of Alzheimer's disease, treatment strategies have largely focused on two problematic proteins, β-amyloid and tau, which form aggregates in the brains of afflicted patients. However, iron accumulation is one of the earliest-reported chemical changes in the Alzheimer's brain, and the enrichment of iron has been documented in amyloid plaques and tau-containing neurofibrillary tangles. An increase in iron is found in a specific brain region, the inferior temporal lobe, which is involved in recording memory and is commonly damaged in Alzheimer's disease (*1*). Indeed, amounts of iron in the brain are positively correlated with Alzheimer's progression and cognitive decline. Iron overload is also observed in the brains of Parkinson's disease and ALS patients. Currently, only a few treatments have been shown to slow the progression of Alzheimer's disease in some cases, including antiamyloid therapy and cholinesterase inhibitors. However, there are no effective strategies to cure or slow the progression of Parkinson's disease or ALS. Thus, research focused on regulating ferroptosis could be transformational. For example, the drug Cu^{II}(atsm) [diacetyl-bis(4-methyl-3-thiosemicarbazonato) copper^{II}] can counter iron-driven neuronal ferroptosis by neutralizing reactive oxygen species that otherwise damage membranes. Cu^{II}(atsm) has been tested in clinical trials for ALS and Parkinson's disease (*2*). Cu^{II}(atsm) can access the brain and be taken orally, which makes it a desirable candidate for neurological disorders in which ferroptosis might be a driving mechanism. Additional compounds that act through this mechanism are in development for other ferroptosis-associated degenerative diseases, including Huntington's disease and Friedreich's ataxia.

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Another mechanism by which ferroptosis drives neurodegeneration is through the death of iron-rich microglial cells. Microglia are resident immune cells of the brain that respond to damage and pathogens. A subpopulation of microglia with a ferroptosis-associated gene expression signature is observed in the brains of Parkinson's patients (*3*). Profiling this signature in patient blood samples may be useful for disease diagnosis. For example, increased expression of the gene *SEC24B* in microglia has been observed in ALS and Alzheimer's patients. SEC24B participates in vesicle trafficking and contributes to iron homeostasis. Thus, targeting this protein in microglia may be an effective therapeutic approach for certain neurodegenerative disorders.

In contrast to neurodegenerative disease contexts where a therapeutic strategy aims to inhibit ferroptosis, selective induction of ferroptosis is gaining momentum as an approach to treating some cancers. For example, lung and colorectal cancers that have developed drug tolerance to common chemotherapeutics display high sensitivity to ferroptosis (*4*). This observation raises the prospect of stimulating ferroptosis in cancers that acquire chemotherapy resistance.

Interventions that affect fatty acid metabolism constitute another approach to inducing ferroptosis in cancer cells. In a whole-genome activation screen of human fibrosarcoma cells (which artificially increased the expression of each gene systematically under ferroptosis conditions), two proteins were found to suppress ferroptosis by modulating phospholipids in the membrane (*5*). These proteins, membrane-bound O-acetyltransferase 1 and 2 (MBOAT1 and MBOAT2), support the cellular metabolism of ferroptosis-blocking monounsaturated fatty acids, such as oleic acid. Some hormone-dependent subtypes of prostate and breast cancers up-regulate the expression of these proteins, which leads to increased protection of cellular membranes against ferroptosis. Antihormone therapy that targets androgen and estrogen receptors sensitizes prostate and breast cancer cells, respectively, to ferroptosis by blocking oleic acid incorporation into membranes and promoting ferroptosis, thereby improving patient survival.

T cell–derived signaling molecules can trigger ferroptosis in cancer cells, as observed in human and mouse melanoma models (*6*). T cells, particularly CD8+ T cells, release the cytokine interferon-γ. This factor stimulates the enzyme ACSL4 (acyl-CoA synthetase long-chain family member 4) within the cancer cell. ACSL4 supports the incorporation of arachidonic acid—a ferroptosis-promoting polyunsaturated fatty acid found in the tumor microenvironment—into cancer cell membranes. Sensitizing tumors in this way could be a goal for cancer immunotherapy.

Beyond cancer and neurodegenerative

[1]Department of Biological Sciences, Columbia University, New York, NY, USA. [2]Department of Chemistry, Columbia University, New York, NY, USA. [3]Department of Pathology and Cell Biology, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY, USA. [4]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA. Email: bstockwell@columbia.edu

disease, ferroptosis may also have implications in the injury of distinct organs, including the lungs, intestines, bones, and blood (see the figure). These observations raise the possibility of developing new treatments for a variety of debilitating conditions. In the lung disorder chronic obstructive pulmonary disease (COPD), for example, cigarette smoke exposure promotes the accumulation of iron in epithelial cells that line the airway. Iron release from the iron storage protein ferritin promotes ferroptosis (*7*). Moreover, lung samples from COPD patients display lower expression of the ferroptosis-protective enzyme GPX4 (which reduces lipid peroxides in membranes) and higher expression of ferroptosis-promoting proteins (such as nuclear receptor coactivator 4) compared with samples from nonsmokers and non-COPD smokers. Thus, blocking ferroptosis in lung epithelial cells could reduce COPD symptoms and improve airflow.

Epithelial cells that line the intestines are also prone to impaired GPX4 function, as seen in patients with Crohn's disease. This disorder is an inflammatory bowel condition thought to be related to diets that are high in polyunsaturated fatty acids, such as arachidonic acid, that are prone to oxidation (*8*). In mice genetically engineered to lack this enzyme in intestinal epithelial cells, polyunsaturated fatty acids triggered mucosal enteritis (intestinal inflammation). This suggests that mechanisms of ferroptosis may play an important role in Crohn's disease progression.

A functional GPX4 enzyme requires the antioxidant glutathione to repair oxidized lipids. Glutathione biosynthesis in turn requires the amino acid cysteine. Cysteine deficiency can therefore lead to lethal amounts of oxidized phospholipids. Low concentrations of cysteine are indeed associated with various diseases that bear the hallmarks of ferroptosis, including stroke and neurological disorders. In hemorrhagic stroke, selenium supplementation increased the expression of GPX4 (a selenium-containing protein) and prevented ferroptosis in neurons (*9*). A brain-penetrant peptide that includes selenocysteine overcame delivery and toxicity issues of selenium and improved recovery after brain hemorrhage by inhibiting ferroptosis.

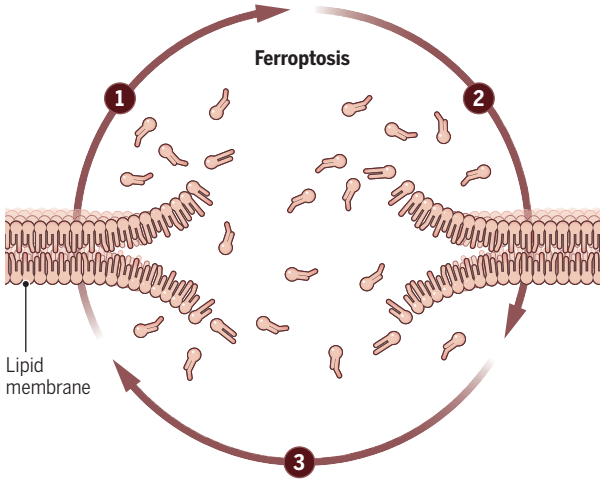
Ferroptosis also affects bone and cartilage development and function. A variation in the GPX4-encoding gene that decreases its activity was identified as a cause for Sedaghatian-type spondylometaphyseal dysplasia (*10*), a rare skeletal and developmental disease. Compounds that inhibit ferroptosis (by repairing the activity of impaired GPX4) improved the survival of fibroblasts derived from these patients, pointing to a potential therapy for this rare disease. Patients with rheumatoid arthritis who suffer from joint destruction could also benefit from controlling ferroptosis. Tumor necrosis factor–α (TNF-α), a proinflammatory cytokine, promotes this disorder by preventing the clearance of damaged cartilage and bone tissues through ferroptosis (*11*). Blocking TNF-α in combination with an agent that stimulates ferroptosis (imidazole ketone erastin) eliminated damaged cells in inflamed tissue of rheumatoid arthritis patients and reduced cartilage and bone damage. Selective induction of ferroptosis in damaged cells thus presents a possible strategy for treating rheumatoid arthritis.

Hemochromatosis is a genetic disorder that disrupts iron absorption and storage, leading to increased iron in the blood. It is mediated by mutations in one of several iron-regulating proteins, including hemochromatosis protein and ferroportin-1. The reactive oxygen species generated by excess iron can manifest as liver cirrhosis. Mouse models of hemochromatosis developed ferroptosis-associated liver damage that could be ameliorated with a ferroptosis inhibitor (ferrostatin-1, a radical trapping agent), showing promise as a strategy for treating organ damage associated with this disease (*12*). When evaluated in mouse models of metabolism-associated fatty liver disease and alcoholic liver disease, which feature lipid oxidation, oxidized peroxiredoxin 3 (PRDX3) was connected to liver damage (*13*). PRDX3 is a repair enzyme that eliminates peroxides, and its oxidation is indicative of ferroptosis. Fibroblasts lacking PRDX3 are resistant to ferroptosis but are resensitized to ferroptosis when PRDX3 expression is restored. These findings pave the way to further investigative therapeutics for chronic liver diseases.

Identifying new strategies to inhibit ferroptosis offers therapeutic promise in contexts where ferroptotic cell death contributes to disease progression. By contrast, selective induction of ferroptosis is a promising approach in cancer therapeutics. Continuing discoveries about the mechanisms governing ferroptosis are likely to improve our understanding of disease biology and provide ideas that may assist in the diagnosis and treatment of diverse human maladies. ■

Biological processes involved in ferroptosis and disease

Ferroptosis is regulated by multiple cellular metabolic pathways, including lipid biosynthesis, iron homeostasis, and antioxidant defense. Modulating these pathways holds promise for treating several associated pathological conditions that affect organs and tissues throughout the body.



1 Lipid biosynthesis
- Breast cancer
- Prostate cancer
- Chemo-resistant cancers
- Crohn's disease
- Chronic kidney disease

2 Iron homeostasis
- Hereditary hemochromatosis
- Chronic obstructive pulmonary disease
- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Parkinson's disease

3 Antioxidant defense
- Sedaghatian-type spondylometaphyseal dysplasia
- Intracerebral hemorrhage

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